REMARKS

Claims 1-40 have been cancelled and new claims 41-69 have been added. Applicant reserves the right to prosecute the subject matter of cancelled claims in further applications.

Support for new claim 41 is found in originally filed claim 1. Support for new claims 42-45 is found in originally filed claims 38, 10 and 26, respectively; support for new claims 45-47 is found in originally filed claims 2, 3 and 4, respectively; support for new claims 48 and 49 is found in originally filed claim 7; support for new claims 50-51, 52-54, 55-56, and 57 is found in originally filed claims 8-9, 12-14, 16-17 and 40, respectively; support for new claims 58 and 59 is found in originally filed claims 29 and 11, respectively; support for new claims 60 and 61 is found in originally filed claims 15 and 19, respectively; claim 66 finds support in originally filed claims 21 and 28; support for claim 63 is found in originally filed claim 24; support for claims 64, 65, 66, 67, 68 and 69 is found in originally filed claims 31, 27, 21, 39, 40,and 59, respectively.

Additional support for the amendments to claim 1 can be found, for example, in claim 6 ("RNA amplification assay"), in paragraphs [0017] and [0019] (also for "urine"), in paragraph [0021], at paragraph [0045] "high stringency conditions" of the application as filed. Support for "comprising at least one prostate cell" can be found in paragraph [0124] and in particular at lines 19-22 of the application as filed. Support for the recitation "nucleic acid extract thereof" can also be found at paragraph [0124] at lines 12-15, in paragraphs [0024], [0026], [0073] and [0124] and in particular between lines 14-20 of the application as filed. In addition, claim 1 has been amended to recite that the detection of PCA3 is correlated to a normal or non-malignant state of the prostate. Support for this amendment can be found in paragraph [0082], on page 35, lines 3-7; on page 39 (paragraph [0091]), lines 17-19 and in paragraph [0105] of the application as filed. Further support for claims 65 and 66 can be found in paragraph [0025] at page 8, ["mixed urine and sperm (e.g., first urine sample following ejaculation)"], and at page 32, lines 2-4 (paragraph [0073]) of the application as filed. Support for new claim 67 is found in originally filed claim 41, except that it integrates the recitation of the

"predetermined cut-off value" found in claim 1 as well as a more precise definition thereof. Further support for claim 67 can be found in paragraph [0071] (at page 31). Support for new claim 68, dependent on claim 41, is found in originally filed claim 29. Finally, support for new claim 69 is found in claim 59.

Reconsideration in view of the following remarks and entry of the foregoing amendments are respectfully requested.

OBJECTIONS

Claim 41 recites "A method for determining a predisposition for, or presence of prostate cancer", as per the Examiner's suggestion concerning claim 1.

The typographical error "chimiluminescence" previously found in claims 10 and 39 has been corrected as suggested by the Examiner. The term "chimiluminescence" no longer appears in the claims and therefore it is requested that the objection be withdrawn.

The expression "...a primer pair composed of SEQ ID NOs..." previously found in claims 9 and 14 has been replaced in claims 51 and 54 by the expression "...a primer pair comprised of the polynucleotide sequences set forth in SEQ ID NOs...", thereby obviating the objection of the Examiner.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The rejection of claims 1-29, 38 and 40 under 35 U.S.C. § 112, second paragraph as being allegedly indefinite for reciting the expression "a predetermined cut off value" is respectfully traversed. Claims 1-29, 38 and 40 have been cancelled, rendering this rejection moot. Further, new claim 67 is submitted to better define "a predetermined cut off value". In view of the foregoing, Applicant respectfully requests that the objection be withdrawn.

The rejection of claims 1-29, 38 and 40 as being allegedly incomplete for omitting essential steps is respectfully traversed. Claims 1-29, 38 and 40 have been cancelled, rendering this rejection moot. Further, new claims 41 and 67 recite a correlation step. In view of the foregoing, Applicant respectfully requests that the objection be withdrawn.

Claims 1-29, 38 and 40 have been rejected as being allegedly indefinite for reciting the expression "high stringency conditions." Claims 41 and 67 define the high stringency conditions for hybridization. In view of the foregoing, Applicant respectfully requests that the objection be withdrawn.

Claim 1 and dependent claims 2-29, 38 and 40 were also rejected because of the recitation "a polynucleotides according to SEQ ID...". These rejections have been rendered moot by the filing of the instant amendment which avoids this terminology.

The rejections of claims 4 and 19 on the basis that there is insufficient antecedent basis for the terms "said PSA sequence" and "said at least one prostate cell", respectively, is respectfully traversed and has been rendered moot by the cancellation of claims 4 and 19. In view of the foregoing, Applicant respectfully requests that the objection be withdrawn.

The rejection of claim 29 as being allegedly indefinite for reciting the expression "homogenous detection method" is respectfully traversed. Applicant respectfully disagrees and submits that this expression is very well-known in the art (see, for example, David E. Burns, Molecular testing in Laboratory Medicine – Selections from Clinical Chemistry, 1998-2001, pages 7-8; and Helen Lee et al., 1997 Nucleic Acid Amplification Technologies, page 144) and that the skilled person would clearly understand its meaning. Moreover, at page 22, lines 2-3, Applicant provides references which describe in detail homogenous detectable methods. In view of the foregoing, Applicant respectfully requests that the objection be withdrawn.

The rejection of claim 37 and dependent claim 38 as allegedly being indefinite for reciting the expression "a prostate cancer specific PCA3 sequence" is respectfully

traversed. This rejection has been rendered moot by the cancellation of these claims and the present amendment.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The rejection of claims 1, 4, 12, 16 and dependent claims 2, 3, 5-11, 13-15, 17-29, 38 and 40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement is respectfully traversed. The recited claims have been cancelled, rendering this rejection moot. Moreover, claims 41 and 67 now recite the high stringency conditions under which the oligonucleotides hybridize to PCA polynucleotides or to second prostate-specific polynucleotide (including human kallikrein 2), therefore providing distinguishing identifying characteristics of the claimed hybridizing sequences. In view of the foregoing, Applicants respectfully submits that the specification provides adequate written description of the claimed oligonucleotides and respectfully submits that the rejection be withdrawn.

The rejection of claims 37 and 39 as allegedly failing to comply with the written description requirement is respectfully traversed. This rejection has been rendered moot by the cancellation of claim 37 and the insertion of hybridization language and nucleic acid sequences in all the independent claims.

The rejection of claims 1-29, 38 and 40 as allegedly failing to comply with the written description requirement concerning the biological sample is respectfully traversed. In view of advancing the prosecution, claims 41 and 67 recite that the biological sample is a urine sample, to recite the high stringency conditions under which the oligonucleotides hybridize to PCA3 polynucleotides or to second prostate-specific polynucleotides and to define the predetermined cut off value (in claim 67; this terminology not being present in claim 41). In view of the fact that the Examiner is of the opinion that the specification is enabled for "a method for determining a predisposition for and the presence of prostate cancer in a patient...from urine...with oligonucleotides that hybridize under high stringency to a polynucleotide encoding PSA...", Applicant respectfully submits that the specification provides sufficient guidance to the skilled

person to determine with predictability that the method would function as claimed, without undue experimentation, and respectfully requests that the objection be withdrawn.

Applicant further respectfully submits that a skilled artisan can, without undue experimentation, design oligonucleotides and molecular beacons that would be specific and useful in detecting or determining a predisposition to develop prostate cancer in accordance with the present invention, based on the known PCA3 and PSA sequences, as well as the second prostate-specific polynucleotides known and described for instance in paragraphs [0102] and [0106] of the present invention. Applicant respectfully submits that in accordance with the present invention in paragraph [106], "Of course, different primer pairs (and probes) can be designed from any part of the PCA3 sequences (SEQ ID NOs: 7, 8, 9, 10 and 13) as well as from the sequence of PSA (genbank accession number M27274, SEQ ID NO11) or any other chosen second prostate specific marker (e.g., KLK2 (genbank acc. No. NM005551), PSMA (genbank acc. No. BC025672), transglutaminase 4 (genbank acc. No.BC007003), acid phosphatase (genbank acc. No. BC016344), PCGEM 1 (genbank acc. No. AF223389)). Applicant respectfully submits that since the sequences targeted by the oligonucleotides, beacons and the like are known, there would not be any undue experimentation in selecting primer pairs, beacons or the like.

With respect to the predetermined cut off value, Applicant respectfully submits that the skilled artisan could determine an appropriate cut off value based on particular needs of sensitivity, specificity and a particular population, for example without undue experimentation. By definition, a predetermined cut off value can be chosen to suit particular needs. The skilled artisan will simply choose a value or range based on particular needs that is associated with prostate cancer or lack of prostate cancer. A definition of "cut off value" is given in paragraph [0071]. In addition, one selected cut off value is exemplified in paragraph [0174]. It should be noted that cut off values are routinely used world-wide in different diagnostic tests, such as in PSA protein detection in serum (e.g., 4.0 ng/ml; between 4.0-10.0 ng/ml...).

In view of the above and foregoing, Applicant respectfully submits that the claims are enabled and requests that the Examiner withdraws the rejection of the claims under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 102

Claims 1-8, 10, 18-20, 22, 25, 26, 28, 29 and 37-40 have been rejected as being allegedly anticipated by Bussemakers *et al.* (US Patent 7,008,765 B1) under 35 U.S.C. § 102(e). Applicant respectfully disagrees and traverses the rejection as follows.

The Office has not shown that Bussemakers discloses a method comprising detecting an amount of PCA3 RNA and second prostate specific RNA. The Office refers to Example 2 (pages 68-70) which allegedly teaches a method wherein PSM or PSA nucleic acid is detected. Applicant respectfully submits that Example 2 provides a head-to-head comparison of the capacity of PCA3 and PSA expression ([or PSM] assessed independently, in separate methods) to distinguish between benign and malignant specimens (see column 36, lines 57-67). Bussemakers affirms that PCA3, but not PSA or PSM, can distinguish between benign and malignant specimens.

Applicant fails to identify where in column 36 of Bussemakers there is a teaching that amplification of PCA3 and said second prostate specific nucleic acid would validate a negative result with PCA3.

The methods of the present invention require a detection of a second prostate-specific nucleic acid, which enables a confirmation that the urine sample contains at least one prostate cell. This is particularly important in cases where PCA3 is not detected.

It should be clear that the detection of a second prostate-specific marker or nucleic acid in a urine sample serves quite a different purpose than the comparison in malignant and non-malignant tissues of the levels of mRNA PCA3 expression with those of another marker for prostate cancer, such as PSA or PSMA.

REJECTION UNDER 35 U.S.C. § 103

All claims except claims 9, 13, 14 and 17 have been rejected as allegedly being unpatentable over Bussemakers in view of a number of cited references under 35 U.S.C. § 103(a). The Office is respectfully referred to the above comments concerning the teaching or suggestion of Bussemakers to combine an RNA amplification of PCA3 and RNA amplification of a second prostate-specific mRNA.

Applicant respectfully submits that the Office has not shown that Bussemakers teaches detecting PCA3 and a second prostate-specific marker from a urine sample in order to diagnose or prognose prostate cancer in a patient. Moreover, the Office has not shown that detection of PSA or other kallikrein family member together with PCA3 is taught by Bussemakers.

Claims 1-8, 10, 11, 15, 18-20, 22, 25, 26, 28, 29 and 37-40 have been rejected as being allegedly unpatentable over Bussemakers *et al.,* in view of Baret (EP 0 256 932 A2). Applicant respectfully traverses the rejection as follows. The Office has not demonstrated that Baret, which is concerned with chemiluminescent assays, teaches or suggests what the Office did not demonstrate was in Bussemakers. In addition, it is the Applicant's belief that prior to the present invention, the use of a quantitative assay to measure PCA3 and a second prostate-specific marker in urine had not been taught.

The rejection of claims 1-8, 10, 12, 16, 18-20, 22, 25, 26, 28, 29 and 37-40 as allegedly being unpatentable over Bussemakers *et al.,* in view of Schlegel *et al.*, (US 2002/0168638 A1) is respectfully traversed. Schlegel fails to show or suggest a combination of a detection of PCA3 RNA and a second prostate specific RNA, a use of such a combination to validate a negative result with PCA3 detection, results in a urine sample, results showing a detection of mRNA in urine. Withdrawal of this rejection is therefore respectfully requested.

The rejection of claims 1-8, 10, 18-20, 22, 24-26, 28, 29 and 37-40 as allegedly being unpatentable over Bussemakers *et al.,* in view of Schlegel *et al.*, (US 2002/0168638

A1) and in further view of Goessl *et al.*, (Cancer Research, 11/1/00, 60: 5941-5945) is respectfully traversed. Goessl allegedly teaches that GSTP1 DNA, a marker associated with prostate carcinoma, can be detected in urine. However, the Office has not shown that Schlegel, alone or together with Bussemakers, teaches a method for detecting prostate cancer in urine based on an RNA amplification of PCA3 and a second prostate specific marker.

Claims 1-8, 10, 18-22, 25, 26, 28, 29 and 37-40 have been rejected as being allegedly unpatentable over Bussemakers *et al.* in view of Cheung *et al.* (Journal of Clinical Microbiology, 10/94, 2593-2597). Applicant respectfully traverses the rejection as follows. Cheung, which is concerned with the use of silica particles for nucleic acid purification, does not correct the defects of Bussemakers in teaching a method for detecting prostate cancer in urine based on an RNA amplification of PCA3 and a second prostate specific marker. In view of the above and foregoing, the combination of Bussemakers with Schlegel and Goessl does not render the claimed methods of the invention obvious.

Finally, claims 1-8, 10, 18-22, 25, 26, 28, 29 and 37-40 have been rejected as allegedly being unpatentable over Bussemakers *et al.,* in view of Strickler *et al.*, (Cancer Epidemiology, Biomarkers & Prevention, 5/01, 10: 523-533). Applicant respectfully traverses the rejection as follows. Strickler is concerned with the detection of SV40 DNA. Strickler does not teach a method for detecting prostate cancer in urine, based on an RNA amplification of PCA3 and a second prostate specific marker.

Applicants respectfully submit that, as per §2143.03 of the MPEP, in order "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art". Because the cited references, either alone or in combination, do not teach or suggest a method combining the detection of both PCA3 RNA and a second prostate-specific RNA in urine to identify a predisposition for or presence of prostate cancer as recited in instant claims 41 and 67, it does not teach or suggest every element of independent claims 41 and 67. Applicant therefore respectfully submits that *prima facie* obviousness of claims 41 and 67 cannot be established in view of

Bussemakers and the cited art. The dependent claims, are thus also not obvious in view of the above-mentioned references. In view of the foregoing, Applicants respectfully submit that the claims are inventive over the above-mentioned documents, and reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Prompt and favorable consideration of this Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Cynthia M. Bouchez
Attorney for Applicants
Registration No. 47,438

Date: December 22, 2006
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600